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(54) Title: CONTROLLED RELEASE MICROPARTICULATE DELIVERY SYSTEM FOR PROTEINS

(57) Abstract

An improved surface erodible controlled release composition and the manufacturing thereof, for the continuous administration of biologically active proteins or peptide fragments, is described. The biologically active protein is dissolved in water or a suitable solvent, alone or in combination with stabilizing agents. The solution is either lyophilized or spray dried to obtain a free flowing powder. The powder is then sieved to obtain the desired average particle size. The free flowing powder of the protein or the stabilized protein is then incorporated into a biodegradable matrix formed of fatty acid anhydride, fatty acid and/or a salt thereof. Examples using growth hormone and bovine serum albumin demonstrate enhanced release, stability and controlled release properties for the fatty acid anhydride microparticular system.

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CONTROLLED RELEASE MICROPARTICULATE DELIVERY SYSTEM FOR PROTEINS

Background of the Invention

The present invention is in the area of bioerodible controlled release systems for the delivery and administration of labile proteins and peptides.

The concept of using biodegradable matrix systems for the delivery of drugs and therapeutically active agents has been well developed and demonstrated to be clinically useful. A number of methods have been well established for the controlled release of low molecular weight compounds. However, the delivery of high molecular weight compounds, such as biologically active proteins and peptides, has been difficult with the presently investigated hydrophilic or hydrophobic, non-polymeric or polymeric matrices.

Alternative methods or carriers for delivery which correct the deficiencies in these systems have been sought for years. Bioerodible polymeric matrices have shown promise in the development of improved delivery systems. Several polymers have been used, including poly(lactides) and their copolymers with glycolic acid, poly(orthoesters), ethylene vinyl acetate and poly(anhydrides). Ethylene vinyl acetate has worked well for the release of biologically active proteins, but is not practical because it is non-degradable. Poly(lactide/co-glycolide) has not shown much promise because there is a considerable amount of aggregation and denaturation of the protein within the matrix. Poly(anhydrides) and poly(orthoesters) release proteins or peptides, but the release rates and the duration of release obtained were not acceptable.

It would be particularly desirable to develop a microparticulate controlled release delivery system for controlled delivery of biologically active proteins. An example of a biologically active and useful protein that is most effective when delivered continuously over extended periods of time is growth hormone. Unfortunately, this protein frequently aggregates, denatures

and loses activity, within the matrix or during the preparation of the delivery system, making it difficult to deliver on a continuous basis.

A controlled release polymer implant system that has been developed to deliver growth hormone is described in European Patent Application No. 86305431.8 which discloses a sustained release microcapsule that contains the protein or peptide, an organic base substance as a drug retaining substance, and wherein the microcapsule wall is made of a polymer. This system has several drawbacks. For example, because the device is not biodegradable, the device must be removed after treatment. Furthermore, the polymer utilized to form the device is limited to those which do not bind to nor promote aggregation of the protein. This limitation in the choice of the polymer also limits the range, type and extent of release of active agent. Polymers which might otherwise be desirable for reasons of release kinetics and duration, specifically polymers that are more hydrophilic or hydrophobic in nature, cannot be used due to interactions with, or adverse influence upon, the biologically active protein. The device is also limited to subcutaneous implantation in animals since use in humans would require post treatment removal of the device.

It is therefore an object of the present invention to provide a biodegradable controlled release microparticulate, injectable delivery system for controlled *in vivo* administration of proteins such as growth hormone.

It is another object of the present invention to provide a method of manufacturing a microparticulate injectable delivery system.

It is yet another object of the present invention to provide a method and means for stabilizing proteins such as growth hormone in biodegradable drug delivery systems, as well as a method of manufacturing a microparticulate injectable delivery system capable of delivering stabilized protein in the biologically active form.

It is still a further object of the present invention to provide a method and means for modulating the rate of release of the parent or stabilized polypeptidic agents from the microparticulate drug delivery system.

Summary of the Invention

An improved surface erodible controlled release composition and the manufacture thereof, for the continuous administration of biologically active proteins or peptide fragments, is described. The biologically active protein is dissolved in water or a suitable solvent, alone or in combination with stabilizing agents. The solution is either lyophilized or spray dried to obtain a free flowing powder. The powder is then sieved to obtain the desired average particle size. The free flowing powder of the protein or the stabilized protein is then incorporated into a biodegradable matrix formed of fatty acid anhydride, fatty acid and/or a salt thereof.

Examples using growth hormone and bovine serum albumin demonstrate the release, stability, and controlled release properties for the fatty acid anhydride microparticular system.

Brief Description of the Drawings

Figure 1 is a graph of the cumulative % release of recombinant bovine somatotropin (rbST) from microparticles formed of palmitic anhydride (squares) and palmitic acid (triangles) over time (hours) at room temperature.

Figure 2 is a graph of the cumulative % release of rbST from microparticles formed of stearic acid (open circles) and stearic anhydride (dark circles) over time (hours) at room temperature.

Figure 3 is the cumulative % release of stabilized rbSt from microparticles formed of stearic anhydride over time (hours) at 37°C, where the stabilizer is Polysorbate™ 80, high pH (squares); sucrose (triangles); Polysorbate™ 80, neutral pH (circles), and potassium carbonate (asterisks).

Figure 4 is the cumulative % release of bovine serum albumin (BSA) from lauric acid microparticles over time (hours) at room temperature.

Figure 5 is a graph of the serum somatotropin level in nanograms/ml in nonlactating heifers over time (days) after subcutaneous injection of Nova A (somatotropin in stearic anhydride with sodium sulfate stabilizer in Miglycol 812).

Figure 6 is a graph of the serum somatotropin level in nanograms/ml in nonlactating heifers over time (days) after subcutaneous injection of Nova B (somatotropin in stearic anhydride with sucrose stabilizer in Miglycol 812).

Detailed Description of the Invention

Controlled release compositions suitable for use in continuously delivering biologically active protein, such as growth hormone and bovine serum albumin, and having enhanced stability with little or no loss of activity, are formed from fatty acid anhydrides microparticles. The biodegradable microparticulate controlled delivery system containing biologically active proteins is useful in a wide range of applications. For example, the controlled release system is useful for controlled and/or enhanced administration of bovine, porcine or human growth hormones to livestock for increased milk production in lactating females and increased growth in maturing animals, as well as administration of growth hormone in human patients.

Proteins

The system is described in detail using bioerodible, biocompatible controlled release microparticulate injectable delivery systems wherein the protein is bovine somatotropic hormone (rbSt) and bovine serum albumin (BSA). The growth hormone is representative of labile proteins which tend to aggregate and BSA is representative of high molecular weight proteins. However, any protein or peptide having therapeutic or biological activity can

be used. The term "biologically active protein" refers to any therapeutically or biologically active protein, protein fragment, peptide, or analog thereof, unless otherwise stated, including proteins, active protein fragments and peptides which are naturally occurring, recombinantly engineered or synthetically produced and which may further undergo various modifications, such as additions to or deletions of amino acids or domains or by glycosylation.

Fatty Acid Anhydrides

The microparticulate carriers are composed of a relatively large amount of fatty acid anhydride monomers or dimers, fatty acid and/or salts thereof. The fatty acid anhydrides include, but not limited to, stearic anhydride, lauric anhydride, and palmitic anhydride. Similarly, fatty acids include, but not limited to, alkane-carboxylic acid, for example lauric acid and/or the salts thereof. The fatty acid anhydrides can be obtained from a variety of commercial sources, such as Aldrich Chemical Co.

Salts of fatty acids have hitherto been used only as a lubricant in an impact tabletting process, but they have never been used in the controlled delivery of biologically active proteins or peptides. Similarly, stearic acid has been used in controlled release preparations, but only for the preparation of granules intended for the oral solid dosage form.

Stabilizing Agents

In the preferred embodiment, a simple surfactant such as polysorbate™ 80 high pH is used both as a stabilizer, to hinder aggregation and to increase the thermal stability of the protein towards denaturation, and to modulate the release rate of the protein from the biodegradable microparticulate controlled delivery system. Other stabilizers include, but are not limited to, simple polysaccharides such as sucrose, deoxycholic acid, sodium azide, polysorbate 80 neutral pH, polyhydric alcohols, and

potassium carbonate. Other protein stabilizing agents are known to those skilled in the art. The most preferred agent is sucrose or sodium sulfate.

The stabilizer causes a substantial increase in the duration of release of the protein and a decrease in initial release rate, when compared to a polymeric matrix formed from a biodegradable polymer in the absence of stabilizer, which permits longer and more uniform therapeutic treatment, without aggregation of the protein. The stabilizing agent has several other effects on the protein. It stabilizes and protects the protein from denaturation, degradation and aggregation, thereby enhancing *in vivo* activity and allowing longer treatment periods between the successive injections. Co-lyophilization or spray drying the solution of protein with the stabilizer also alters both the rate of release and duration of release of the growth hormone from the microparticulate matrix. Significant control of the release rate and the released biological activity is achieved by this combination of stabilizer, protein, and microparticulate carriers.

Method of Preparation

The preferred method of making a controlled release, bioerodible, biocompatible, microparticulate injectable delivery system for the controlled delivery of biologically active protein is as follows.

The biologically active protein is dissolved in an appropriate solvent, such as water. The solution is then lyophilized or spray dried to obtain a free flowing powder. Stabilized protein is obtained by co-lyophilizing or spray drying an aqueous solution of the growth hormone and the stabilizer. The free flowing powder is further reduced in particle size by mild trituration in a mortar with pestle. The powder is then sieved to obtain the desired particle size, ranging generally from 10 to 400 μ, most preferably approximately 100 μ for subcutaneous administration. The protein powder is then melt mixed with the appropriate microparticulate carrier, such as fatty acid anhydride or fatty acid and/or salts thereof. The fatty acid anhydride is

selected based on the denaturation temperature of the protein to be delivered. The resulting melt is solidified by cooling to room temperature and then powdered to the desired particle size, in the range of 100 to 500 μ, using any of the particle size reducing equipment known to those skilled in the art. In general, the ratio of protein to fatty acid anhydride will be in the range of 1% to 50%. When stabilizer is added, it will generally be in the range from 5 to 100 % of the amount of protein.

Alternatively, the powdered and sieved protein is suspended in a solution of the microparticulate carrier. The suspension is spray dried to obtain the final product. The spray dried mixture can be used as an injectable or could be compressed into a device of specific shape for use as an implantable delivery system.

In yet another process, the sieved powder can be dry mixed with the appropriate microparticulate carrier, at the desired loading ratio, and processed by microencapsulation or pressing into an implantable device. The microparticulate product or the devices are preferably stored at -20°C under an inert atmosphere prior to use.

Carriers for *in vivo* Administration

Prolonged *in vivo* activity can be achieved by selecting an appropriate vehicle for suspending and administering the microparticles. The preferred vehicles are the vegetable and/or mineral oils, mono, di or triglycerides like miglyols, and/or any fats and waxes of natural or synthetic origin which are deemed suitable as biocompatible materials.

The present invention is further described with reference to the following non-limiting examples demonstrating the preparation and characterization of microparticles with varying loading.

Example 1: Preparation of microparticles of stearic acid containing recombinant bovine somatotropin (rbSt) by melt mixing.

Microparticles of stearic acid were prepared by combining the spray dried rbSt (20 mg) with stearic acid (80 mg). Spray dried powdered rbSt was added to the stearic acid, which was pre-melted at 75°C. The melt dispersion was mixed thoroughly with a spatula and cast into a thin film. The thin film was then grounded into the particles of the desired average size, approximately 400 μ.

Example 2: Preparation of microparticles of stearic anhydride containing rbSt by solvent method.

A 2% solution (4 ml) of stearic anhydride was prepared by dissolving the stearic anhydride in dichloromethane. Powdered rbSt (20 mg) was added to that solution and a uniform dispersion was obtained by vortexing the suspension. The suspension was cast as a thin film on a glass plate. The solvent was removed from the film using a stream of dry nitrogen gas. After removal of the solvent, particles of stearic anhydride embedded with rbSt were obtained. Residual solvent was completely removed by lyophilizing the particles.

The solvent free particles were powdered into a desired size range for *in vivo* application, approximately 400 μ.

Example 3: Preparation of microparticles of stearic anhydride containing rbSt by spray drying method.

A suspension of rbSt in a solution of stearic anhydride was prepared as described in Example 2. The suspension was spray dried in a Buchi spray dryer to obtain microparticles embedded with rbSt. The average particle size of the microparticles was less than 250 microns.

Example 4: Preparation of microparticles of lauric acid containing bovine serum albumin (BSA) by melt mixing.

Microparticles of stearic acid were prepared by combining the spray dried BSA (20 mg) with lauric acid (80 mg). Spray dried powdered rbSt was added to the lauric acid, which was pre-melted at 45°C. The melt dispersion was mixed thoroughly with a spatula and cast into a thin film. The thin film was then grounded into the particles of the desired average size, approximately 400 μ.

Example 5: Preparation of stabilized rbSt.

The rbSt (150 mg) and stabilizer (37 mg) were dissolved in 200 ml of highly purified water. The solution is then transferred to a lyophilization flask. The solution is pre-frozen using a dry ice/acetone bath and lyophilized by standard methods. The resulting white crystalline powder is then reduced to the desired particle size by triturating it in a mortar with pestle. The stabilizers evaluated were sucrose, potassium carbonate, sodium sulfate, deoxycholic acid and polysorbate 80. In case of polysorbate 80, the amount of rbSt and stabilizer were 100 mg and 5 mg, respectively.

Example 6: Preparation of microparticles of stearic anhydride containing stabilized rbSt.

Microparticles of stearic anhydride were prepared by combining the stabilized rbSt (75 mg), as described in Example 5, with stearic anhydride (300 mg) to obtain 20% w/w loading. Stabilized rbSt was added to the stearic anhydride, which was pre-melted at 75°C. The melt dispersion was mixed thoroughly with a spatula and cast into a thin film. The thin film was then ground into particles of the desired average size. When the rbst was stabilized with polysorbate 80, the amount of stabilized rbSt and stearic anhydride were 50 mg and 200 mg, respectively.

Example 7: **Preparation of microparticles of palmitic acid and palmitic anhydride containing rbSt.**

Microparticles of palmitic acid and palmitic anhydride were prepared by combining spray dried rbSt (75 mg) with palmitic acid (225 mg) and palmitic anhydride (225 mg), respectively. Spray dried powdered rbSt was added to the palmitic acid and palmitic anhydride, which were pre-melted at 65°C. The melt dispersion was mixed thoroughly with a spatula and cast into a thin film. The thin film was then ground into the particles of the desired average size.

Example 8: **Release of spray dried rbSt from the microparticles of palmitic acid and palmitic anhydride.**

Release studies were conducted with the microparticles (125 mg) of palmitic acid and palmitic anhydride containing spray dried rbSt prepared in example 7 by dispersing them in 20 ml of 0.1 M phosphate buffer, pH 7.4. The release study was conducted at 25°C and the entire buffer was changed at appropriate time intervals. The amount of rbSt released was analyzed by size exclusion high pressure liquid chromatography. The release profile is shown in Figure 1.

Example 9: **Release of spray dried rbSt from the microparticles of stearic acid and stearic anhydride.**

Release studies were conducted with the microparticles (125 mg) of stearic acid and stearic anhydride containing spray dried rbSt prepared in example 1 and 3 by dispersing them in 20 ml of 0.1 M phosphate buffer, pH 7.4. The release study was conducted at 25°C and the entire buffer was changed at appropriate time intervals. The amount of rbSt released was analyzed by size exclusion chromatography. The release profile is shown in Figure 2.

Example 10: Release of stabilized rbSt from the microparticles of stearic anhydride.

Release studies were conducted with the microparticles (125 mg) of stearic anhydride containing stabilized rbSt prepared as described in Example 6 by dispersing them in 20 ml of 0.1 M phosphate buffer, pH 7.4. The release study was conducted at 37°C and the entire buffer was changed at appropriate time intervals. The amount of rbSt released was analyzed by size exclusion chromatography. The release profile is shown in Figure 3.

Example 11: Release of BSA from the microparticles of lauric acid.

Release studies were conducted with the microparticles (125 mg) of lauric acid containing spray dried BSA prepared as described in Example 4 by dispersing them in 20 ml of 0.1 M phosphate buffer, pH 7.4. The release study was conducted at 25°C and the entire buffer was changed at appropriate time intervals. The amount of BSA released was analyzed by size exclusion chromatography. The release profile is shown in Figure 4.

The results in the above examples demonstrate that proteins can be incorporated into a microparticulate injectable system formed of fatty acids and fatty acid anhydrides for delivery of biologically active proteins, based on molecular weight determinations of the active monomer (versus the inactive dimer) and by radioimmunoassay. The combination of stabilizer and surface eroding matrix results in more complete release of the protein over an extended period of time. The highest yield and most linear results were obtained by the use of stearic anhydride and lauric acid.

Example 12: In Vivo Release of Somatotropin from Stearic Anhydride in Heifers

Somatotropin was co-lyophilized separately with the stabilizers sodium sulfate and sucrose. The ratio of protein to stabilizer was 2:1. Two samples of stearic anhydride (12.30 grams) were then melted in a mortar at 75°C. To the stearic anhydride samples were added separately 5.25 grams

of the two stabilized growth hormone mixtures, and the new mixtures mixed until they reached room temperature. The particles were triturated lightly and sieved through a 425 micron sieve. The microparticles that passed through the sieve were used for in vivo testing. The microparticles were suspended in Miglyol 812 (Huls Corporation) for subcutaneous injection in non-lactating Holstein heifers. The formulations containing sodium sulfate and sucrose stabilized growth hormone in stearic anhydride were designated Nova A and Nova B, respectively. Blood samples were taken at 0 and 12 hours on the day of injection, and then on days 1, 2, 3, 5, 7, 9, 11, 13, and 15 post-injection. Blood samples were also taken from three control (untreated) heifers at the same time intervals. Blood was allowed to clot at 23° C for one hour, centrifuged at 1500 x g, and the serum decanted and stored at -20° C for radioimmuncassay. The serum somatotropin levels in nanograms/ml over time for Nova A and Nova B are illustrated in Figures 5 and 6, respectively. The serum somatotropin level of non-injected control heifers remained relatively constant at 0.7 ng/ml. As illustrated in both Figures 5 and 6, the serum bovine somatotropin level in the treated heifers peaked at approximately 8-10 ng/ml approximately two days after injection, and remained above normal levels for at least nine days.

Modifications and variations of the fatty acid microparticles for controlled release of proteins will be obvious to those skilled in the art, and are intended to come within the scope of the appended claims.

We claim:

1. A protein delivery microparticle comprising

biologically active protein or peptide dispersed in fatty acid or fatty acid anhydride monomers or dimers.

2. The microparticle of claim 1 wherein the protein to fatty acid or fatty acid anhydride ratio is in the range of between 1:100 and 1:2, by weight of the protein to fatty acid anhydride.

3. The microparticle of claim 1 wherein the protein further comprises a stabilizer.

4. The microparticle of claim 3 wherein the ratio of stabilizer to protein is in the range of between 1:20 to 1:1, by weight of protein.

5. The microparticle of claim 1 wherein the protein is selected from the group of biologically active proteins, protein fragments, and peptides, which are naturally occurring, recombinantly engineered, or synthetically produced.

6. The microparticle of claim 5 wherein the protein is growth hormone.

7. The microparticle of claim 1 wherein the fatty acid or fatty acid anhydrides are selected from the group consisting of stearic anhydride, lauric anhydride, palmitic anhydride, and alkane-carboxylic acid, and salts thereof.

8. The microparticle of claim 1 having a size range of approximately 100 μ.

9. The microparticle of claim 1 further comprising a pharmaceutically acceptable carrier for administration to a human or an animal.

10. The microparticle of claim 9 wherein the carrier is selected from the group consisting of vegetable oils, mineral oils, mono, di or triglycerides, and fats and waxes of natural or synthetic origin.

11. A method for the preparation of a controlled delivery protein microparticle comprising incorporating a biologically active protein or peptide into a microparticle formed of fatty acid or fatty acid anhydride monomers or dimers by the steps of:

providing a dry protein powder;

mixing the protein with melted fatty acid or fatty acid anhydride at a temperature below which the protein denatures; and then

solidifying the melted mixture.

12. The method of claim 11 wherein the protein is dried to form protein particles, then mixed with the fatty acid or fatty acid anhydride.

13. The method of claim 12 wherein the fatty acid or fatty acid anhydride is melted at a temperature below the denaturation temperature of the protein.

14. The method of claim 12 wherein the protein is physically mixed with the fatty acid or fatty acid anhydrides.

15. The method of claim 11 wherein the protein to fatty acid or fatty acid anhydride ratio is in the range of between 1:100 and 1:2, by weight of the protein to fatty acid anhydride.

16. The method of claim 11 further comprising providing a stabilizer with the protein particles.

17. The method of claim 16 wherein the ratio of stabilizer to protein is in the range of between 1:20 to 1:1, by weight of protein.

18. The method of claim 11 further comprising suspending the protein microparticles in a pharmaceutically acceptable carrier for administration to a human or an animal selected from the group consisting of vegetable oils, mineral oils, mono, di or triglycerides, and fats and waxes of natural or synthetic origin.

19. The method of claim 11 wherein the protein is selected from the group of biologically active proteins, protein fragments, and peptides, which are naturally occurring, recombinantly engineered, or synthetically produced.

20. The method of claim 19 wherein the protein is growth hormone.

21. A method for the controlled delivery of a protein comprising administering the protein containing microparticles of claim 1 to a human or an animal.

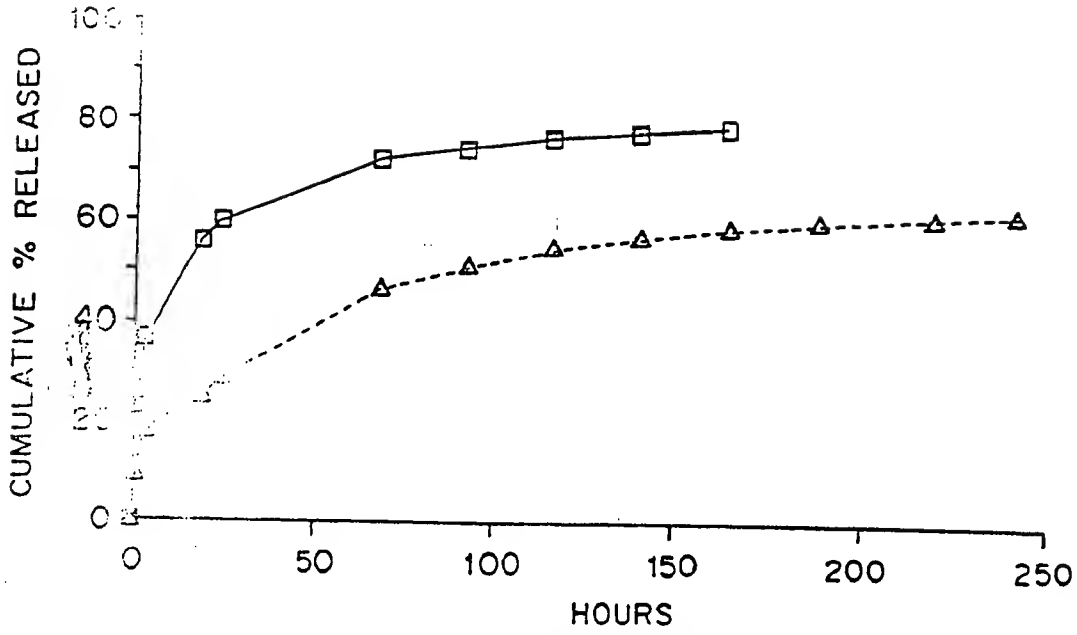

FIGURE 1

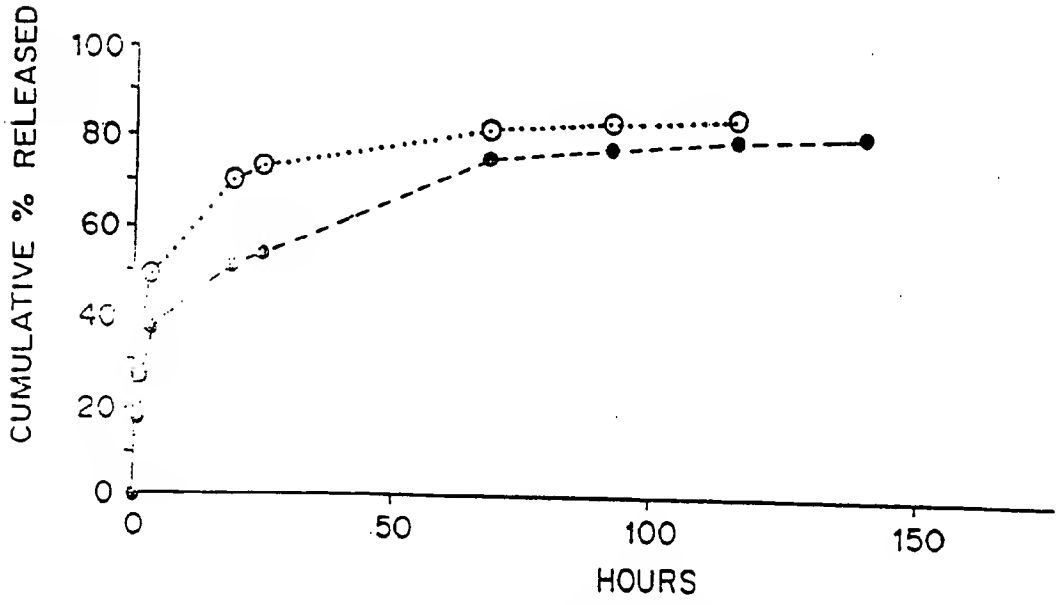

FIGURE 2

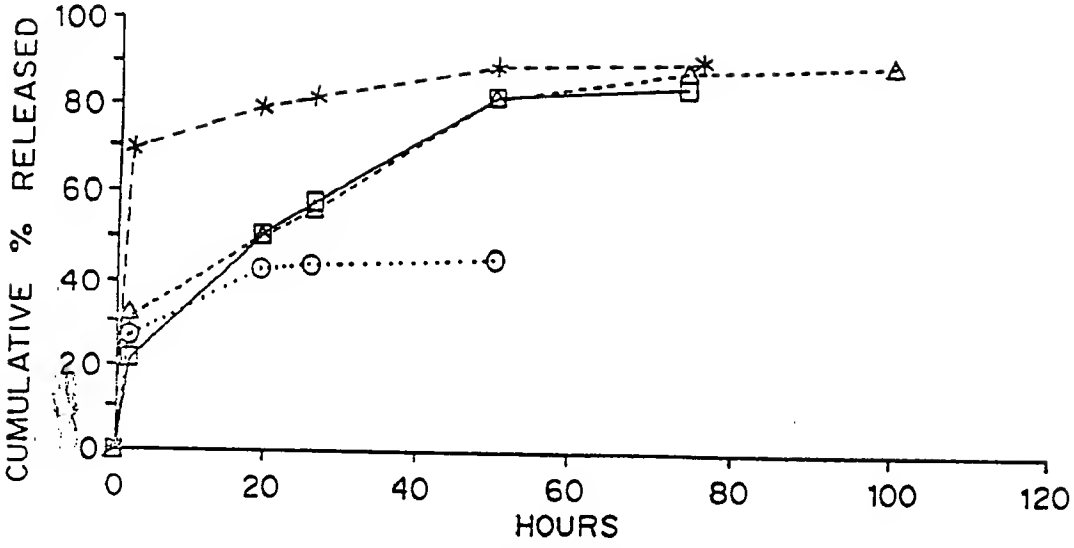

FIGURE 3

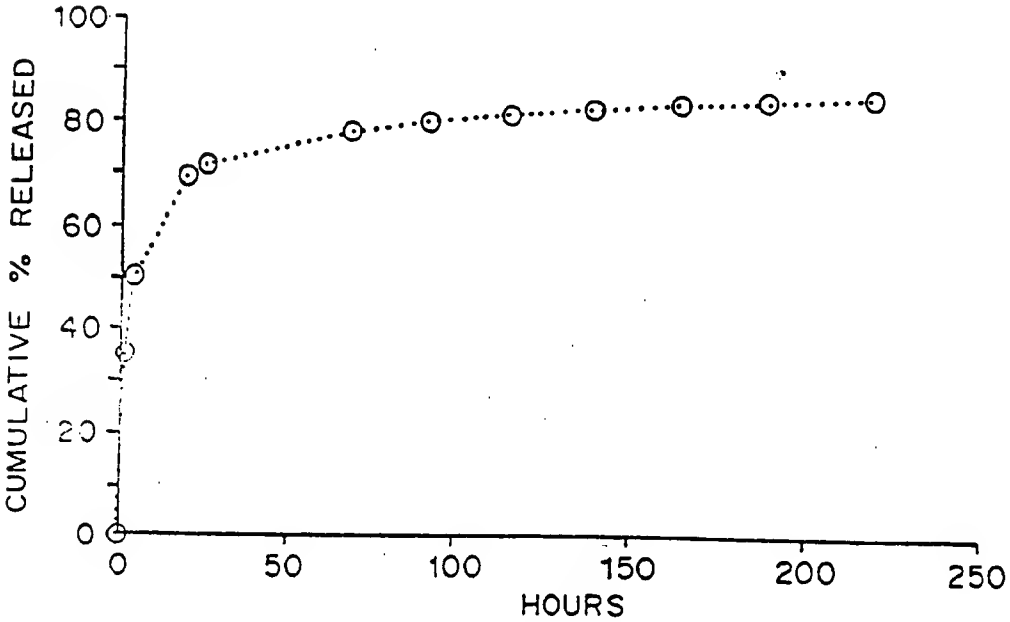

FIGURE 4

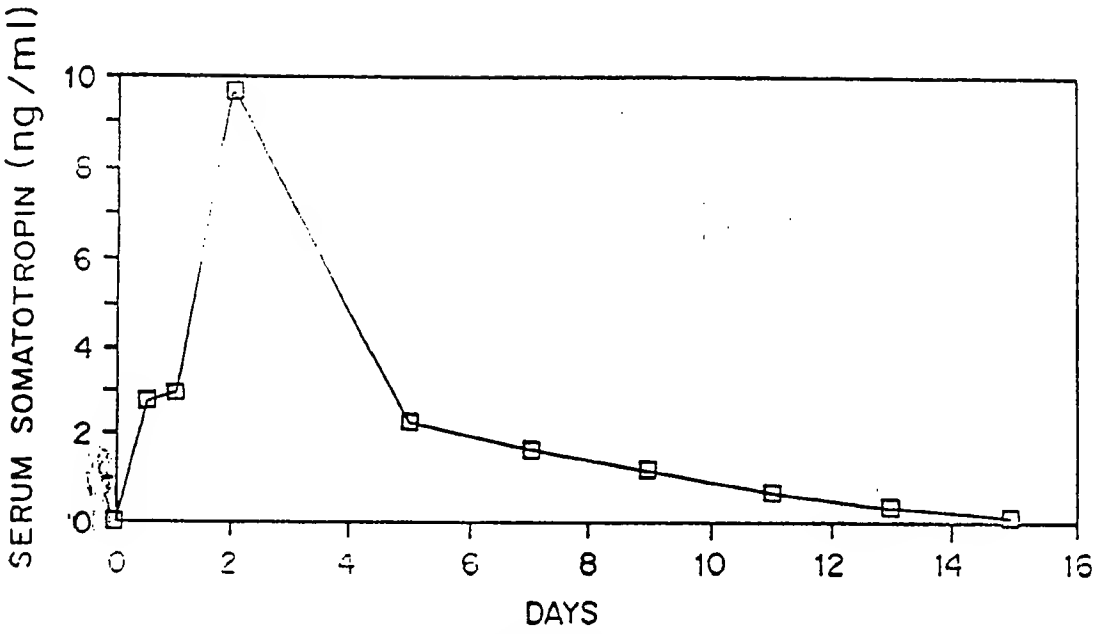

FIGURE 5

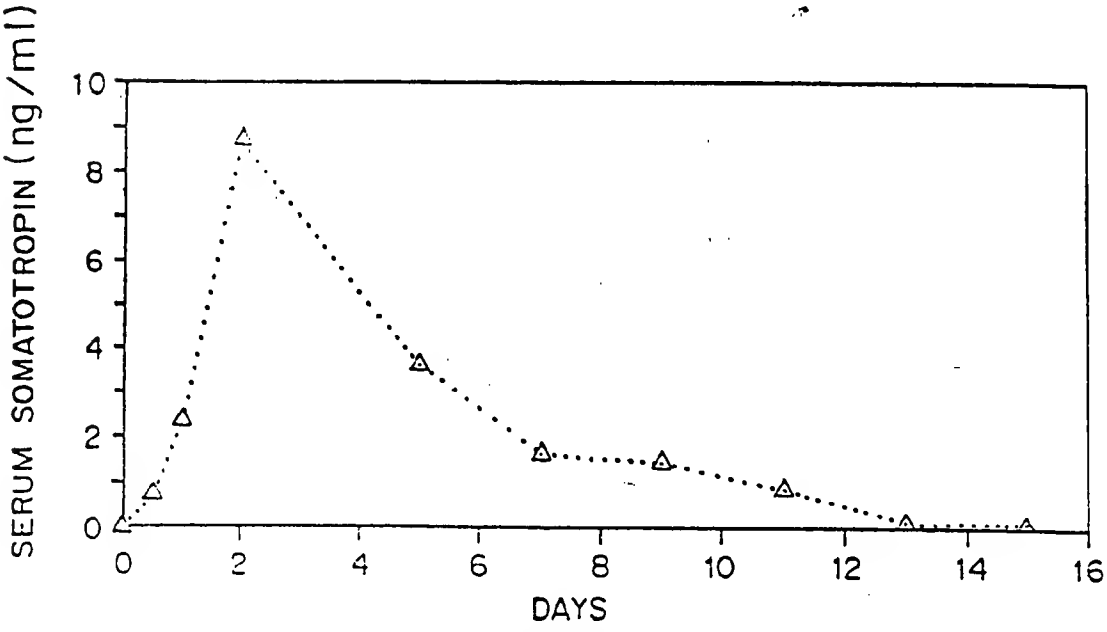

FIGURE 6

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US92/01351

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC [5]: A61K 9/14, 9/16, 37/02, 37/36
US CL : 424/489, 499, 502; 514/2, 12, 21

II. FIELDS SEARCHED

Minimum Documentation Searched[4]

Classification System	Classification Symbols
U.S.	424/489, 499, 502; 514/2, 12, 21

Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched[6]

APS, DIALOG/BIOCHEM of U.S.National Application Serial No. 07/658,089

III. DOCUMENTS CONSIDERED TO BE RELEVANT[14]

Category[15]	Citation of Document,[16] with indication, where appropriate, of the relevant passages[17]	Relevant to Claim No.[18]
X	EP, A, 0,257,368 (Steber et al.) 02 March 1988, see entire document.	1-21
X	EP, A, 0,350,246 (Yoshioka et al.) 10 January 1990, see pages 2-6.	1-21
X	International Journal of Pharmaceutics, Volume 54, issued 1989, P. Y. Wang, "Lipids as Excipient in Sustained Release Insulin Implants", pages 223-230, see entire document.	1-21

* Special categories of cited documents:[16]
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search[2]	Date of Mailing of this International Search Report[2]
[illegible]	04 JUN 1992
International Searching Authority[1]	Signature of Authorized Officer[20]
ISA/US	ANDREW ROZYCKI, EXAMINER GROUP 180

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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE[1]

1. ☐ Claim numbers _, because they relate to subject matter (1) not required to be searched by this Authority, namely:

2. ☐ Claim numbers _, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out (1), specifically:

3. ☐ Claim numbers _, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING[2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Search Authority did not invite payment of any additional fee.

Remark on protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.